

Figure 1

# Summary of Functions for Signal Transduction Transcripts Differentially Expressed in MDD

- GRB2 (growth receptor binding protein 2). An adaptor protein that transduces signal from an activated growth factor receptor, culminating in the activation of Ras.
- ITPKB (inositol-1,4,5-triphosphate-3 kinase B). A member of a family of kinases involved in inositol triphosphate signal transduction.
- PAK-1 (p21 activated kinase 1). A protein that is regulated by small-GTP binding proteins, like Ras, and is believed to directly act on the JNK1/MAP kinase signal transduction cascade.
- PKC, beta1 (protein kinase C, beta 1). A protein kinase involved in several  $\text{Ca}^{++}$  and  $\text{IP}_3$  dependent signal transduction cascades.
- RalGDS (Ral guanine nucleotide dissociation stimulator). Stimulates dissociation of GDP from Ras and Ras-like (Ral) small G-proteins, thereby, increasing the rate of GTP-GDP exchange and facilitating activation of Ras/Ral proteins.
- RAP1 (GTPase activating protein 1). Stimulates GTPase activity of small GTP-binding proteins, thereby terminating their activity and functionally inhibiting Ras/Ral proteins.
- RGS20 (regulator of G-protein signaling 20). A GTPase activating protein that has specificity for the alpha z subunit of heterotrimeric G-proteins. Facilitation of GTPase activity would terminate signal transduction and thus act as a negative regulator.

# bFGF System Transcripts are Differential Expressed in PFC in Subjects with MDD

- Down regulated
- Up regulated
- No Change

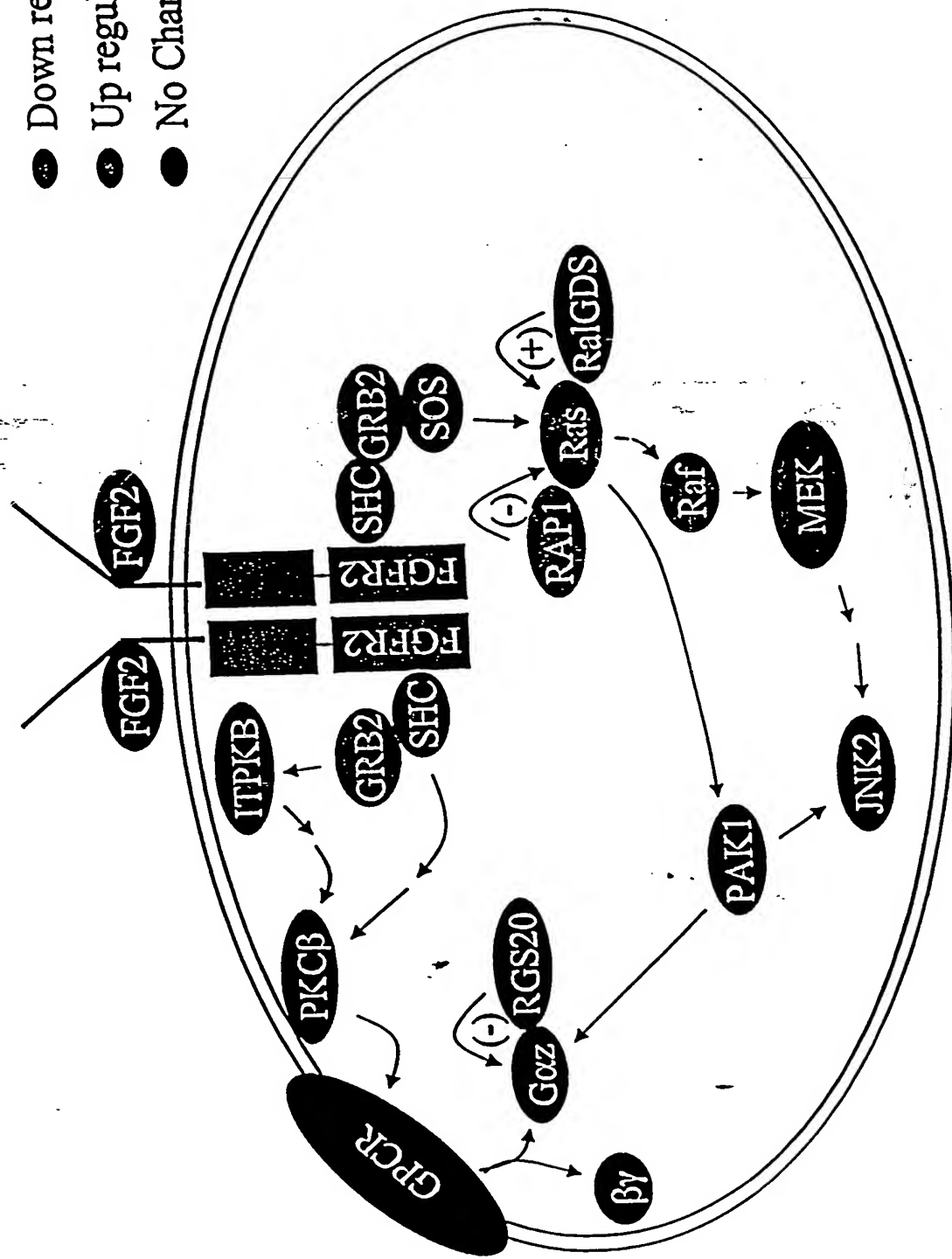


Figure 3

# Fold Change and p-values for bFGF system Transcripts in PFC for MDD Subjects

probe set ID	Gene	Accession #	Fold Change	p-value
1593_at	FGF2	J04513	-1.4	0.04
1363_at	FGFR2	M87770	-1.4	0.02
1143_s_at	FGFR2	M87771	-1.2	0.04
33855_at	GRB2	M96995	1.2	0.06
37272_at	ITPKB	X57206	-1.4	0.05
1557_at	PAK1	U24152	1.4	0.01
1558_g_at	PAK-1	U24152	1.6	0.05
1217_g_at	PKC beta1	X07109	1.6	0.02
36550_at	RalGDS	AL049538	-1.5	0.01
1270_at	RAP1	M64788	1.2	0.06
41086_at	RGS 20	AF060877	-1.6	0.04

Figure 4

Figure 5

# Metabolic pathways significantly dysregulated

Pathway	GS/GOC	possibility of false positive
oxidative phosphorylation	8/35	0.0017
carotenoid biosynthesis	2/5	0.0057
proteasome	3/30	0.0360
ATP synthesis	3/32	0.0425
sterol, vitamin K/E, carotenoid biosynthesis	2/17	0.0643
Parkinson's disease	2/21	0.0934
sphingophospholipid	1/4	0.0955
nitrogen metabolism	2/23	0.1091
galactose metabolism	2/24	0.1172
glutathion metabolism	2/32	0.1866
glycine, serine, threonine methabolism	2/33	0.1957

GS/GOC; genes selected/genes on a chip

Figure 6

# Signaling & Metabolic Pathways Significantly Altered in AnCg of Bipolar Subjects

• 1.	Inositol Phosphate Metabolism	14/135
• 2.	Nicotinate and Nicotinamide Metabolism	11/116
• 3.	Benzoate Degradation N-Ac CoA Ligation	11/118
• 4.	Alanine and Aspartate Metabolism	4/18
• 5.	Starch and Sucrose Metabolism	11/132
• 6.	Sphingoglycolipid Metabolism	11/134
• 7.	Glutamate Metabolism	4/21
• 8.	Phosphotydl-Isositol Signaling	8/101

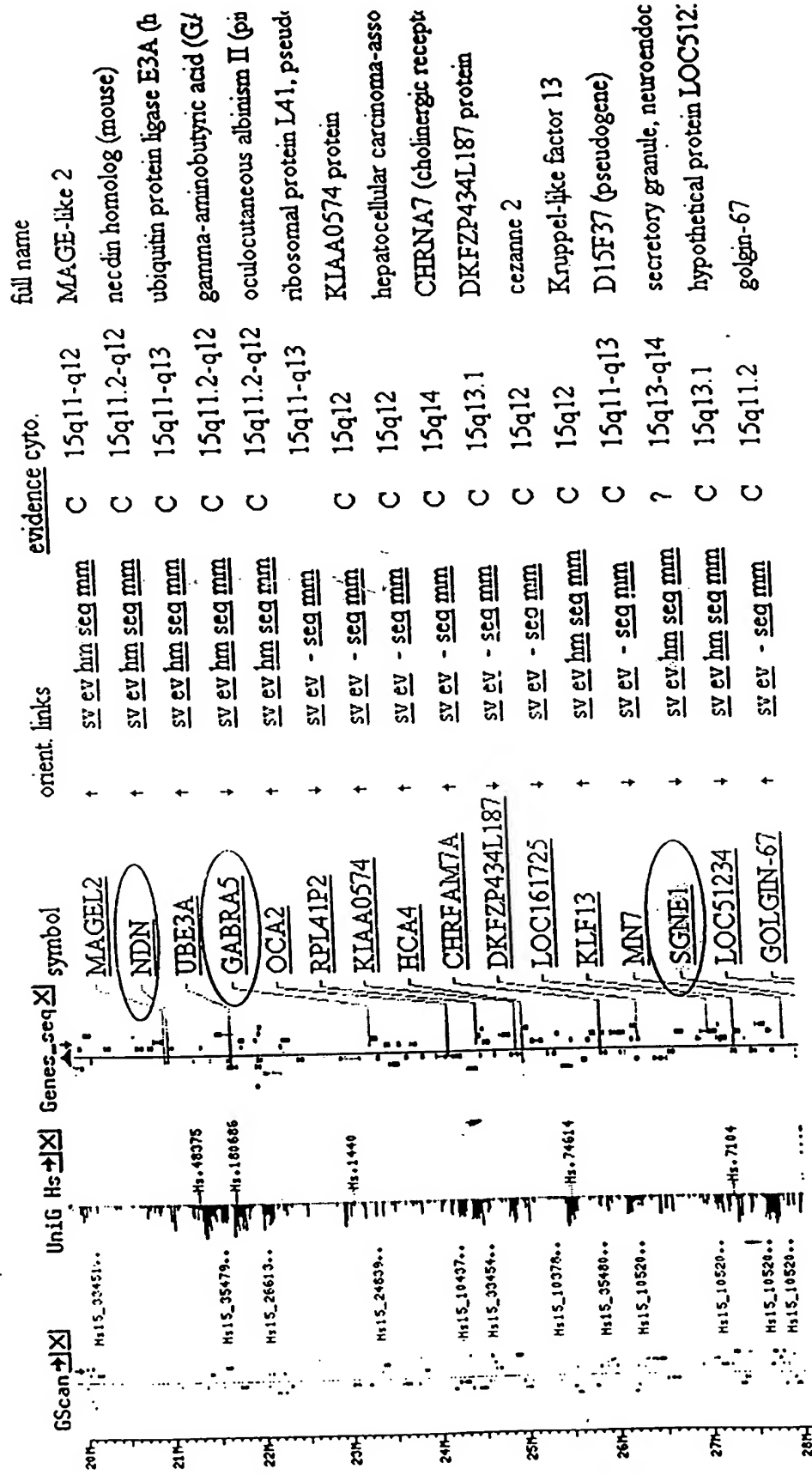
Figure 7

# Three Over Expressed Genes Are Located in the Same Chromosomal Region

Symbol	Description	Cytogenetic Band (Mb)
SGNE1	Secretory granule, neuroendocrine protein 1 (7B2 protein)	15q13
NDN	Necdin homolog (mouse)	15q11.2
GABRA5	Gamma-aminobutyric acid (GABA) A receptor, alpha 5	15q11.2

Figure 8

Three of the 13 genes are on 15q11-13 within the Prader  
Willi region (SGNE1, GABRA5, and NDN)



These 3 genes are found within a 7 Mb region that contains 10 other genes.



Figure 9

Genes Regulated in Human Postmortem Tissue (Dorsolateral PFC and Anterior Cingulate)

Gene	MDD	MDD	BD	BD
neuronal cell adhesion molecule	↓			
solute carrier family 14 (urea transporter) member	↑			
protein kinase C, beta 1	↓	↓		
NEIL-like 1	↓			
phosphoribosyl pyrophosphate synthetase	↓			
solute carrier family 1 (glial high affinity glutamate transporter) member		↑		
glutamate receptor, metabotropic 3				↓
Microtubule Associated Protein 2			↓	
Fibroblast Growth Factor 2		↑		
GABA A Receptor				↓
Inositol 1,4,5-trisphosphate receptor		↓		

# GPCR and cAMP/PI/Rho pathways

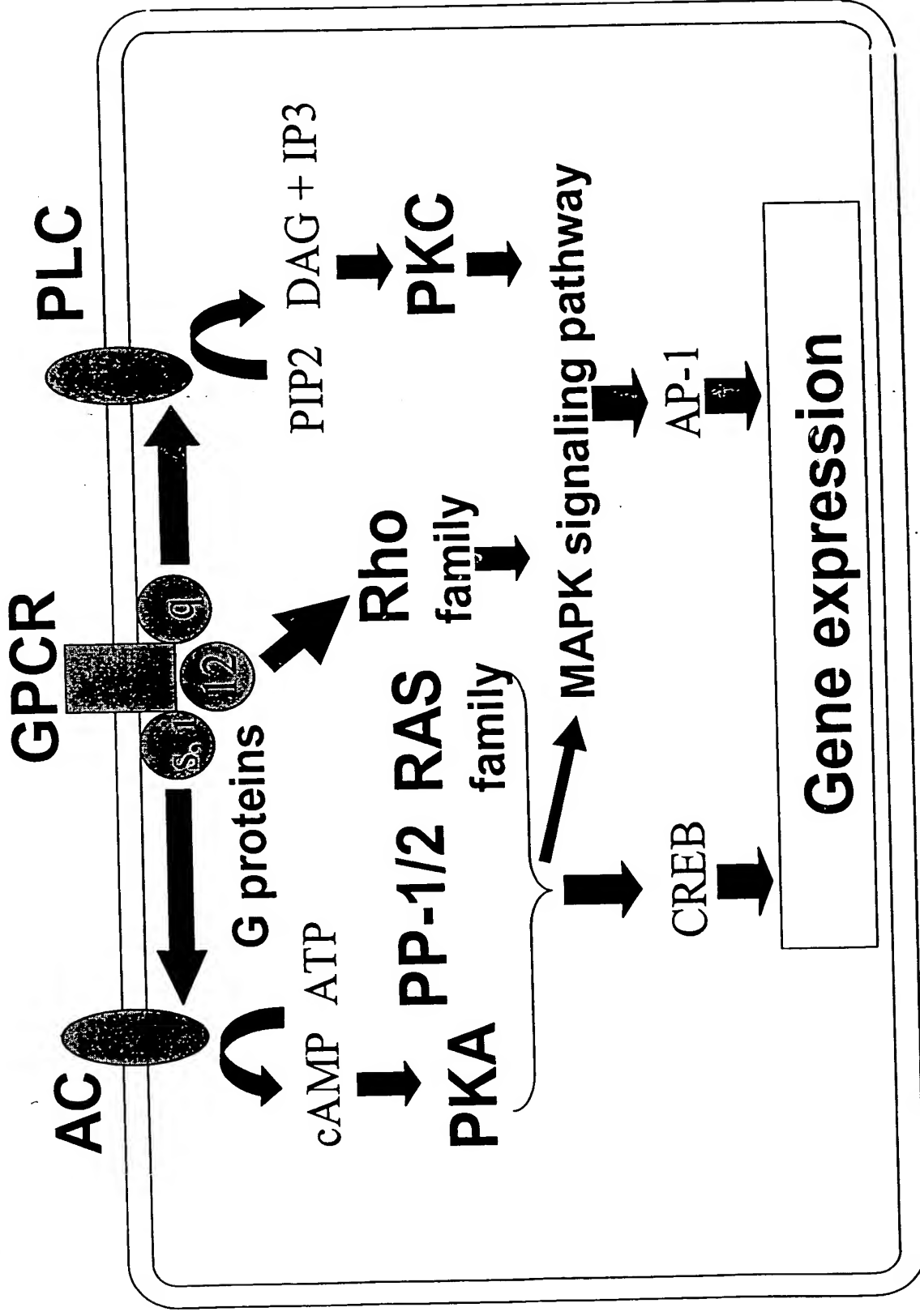


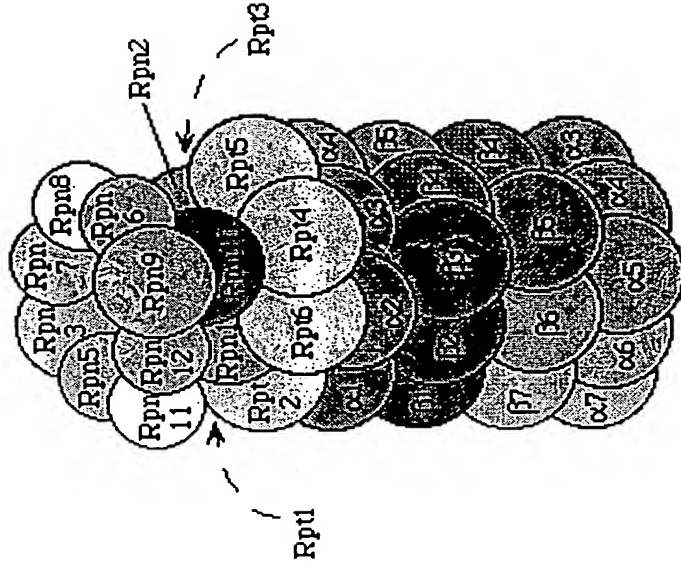
Fig. 10

# Proteasome: Alterations in In Bipolar Ss, Anterior Cingulate

- 28 subunits
- Four rings of seven.
- Outer rings: alpha subunits
- Inner Rings: beta subunits
- Beta: responsible for peptidase activity.
- Degrades Short-lived and Misfolded Proteins
- Role in Ubiquitination
- ATP Dependent Activity

*Note: 11 / 31 genes are significant, mostly Beta*

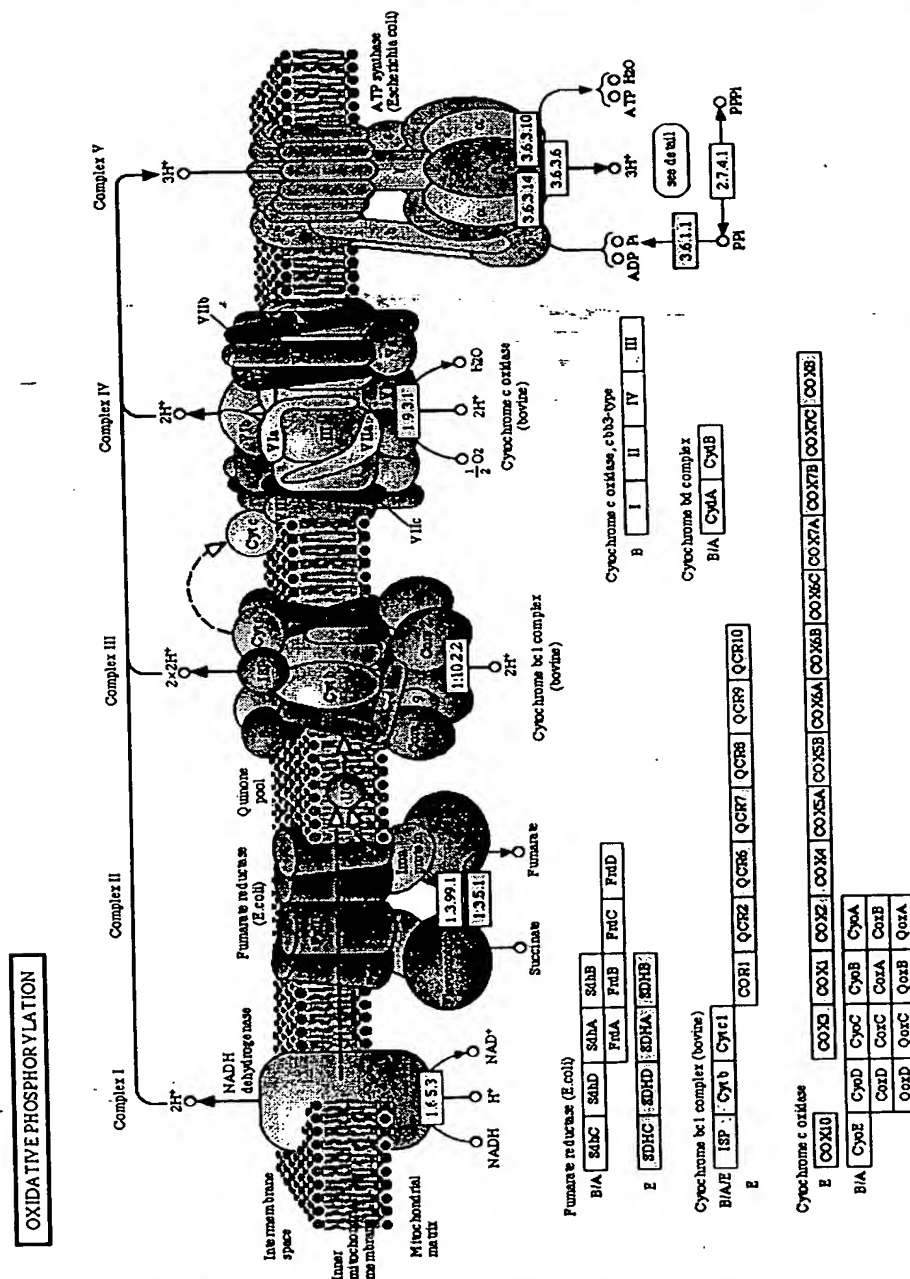
## PROTEASOME



26S Proteasome (Saccharomyces cerevisiae)

Rpn1	Rpn2	Rpn3	Rpn4	Rpn5	Rpn6
Rpn7	Rpn8	Rpn9	Rpn10	Rpn11	Rpn12
Rpt1	Rpt2	Rpt3	Rpt4	Rpt5	Rpt6
$\alpha 1$	$\alpha 2$	$\alpha 3$	$\alpha 4$	$\alpha 5$	$\alpha 6$
$\beta 1$	$\beta 2$	$\beta 3$	$\beta 4$	$\beta 5$	$\beta 6$
					$\alpha 7$
					$\beta 7$

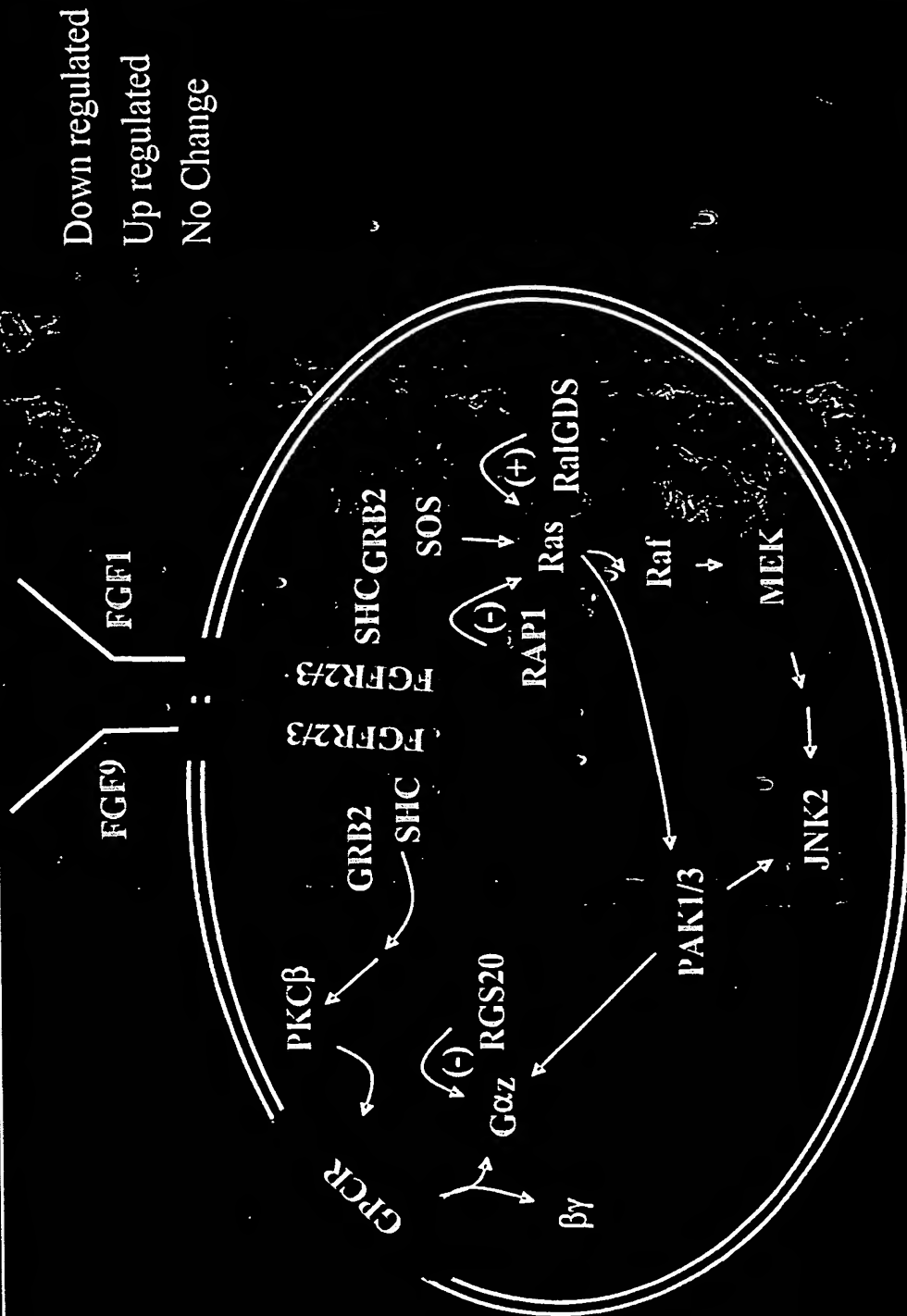
# Oxidative Phosphorylation



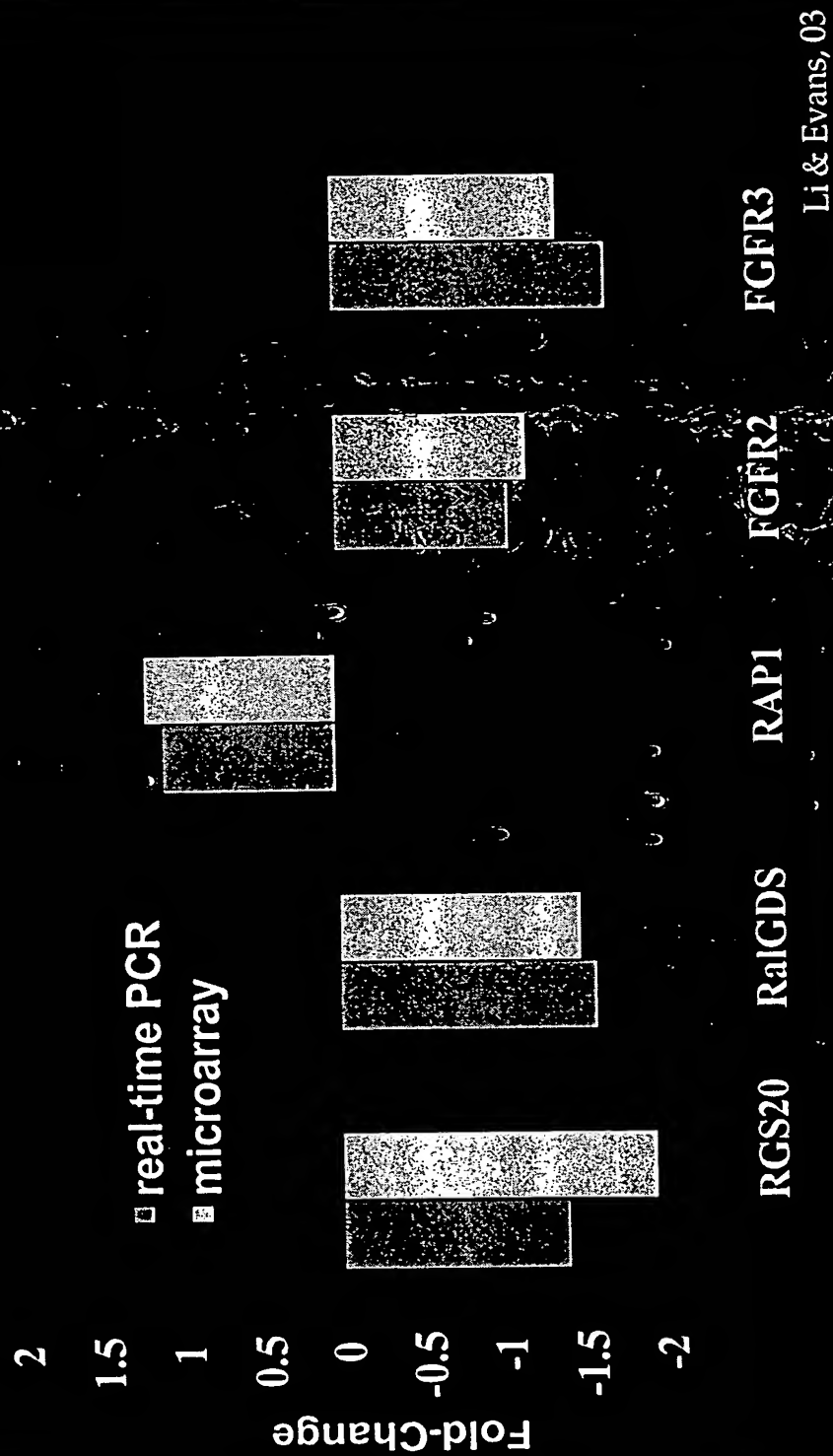
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◆ ATP5A1; ATP6V1A1; ATP6V0E; ATP6V0ENDUFV1; ATP6V1E1; ATP5H; ATP5J;  
ATP6V0B; ATP5O; ATP5J2; ATP6V0D1  
◆ NDUFS7; NDUFB5; NDUFS2; NDUFC1; NDUFB3  
◆ COX7B; SDHB; UQCRC2

# Major Depression, DLPEC: FGF System Transcripts are Altered



# Real-Time PCR Confirms Microarray Results in FGF System



# Signaling Pathways involving GABA & Glutamate

## BPD\_AnCg

- GABRA5
- GRIA1
- GRM3
- GRIA3
- GRIK1

## BPD\_DLPPFC

- GABRA5
- GABBR1
- GABARAPL2
- (None Down)

## MDD\_AnCg

- (None UP)
- SLC1A3
- SLC1A2
- GLUL

Solute carrier family 1 (glial high affinity glut transporter), member 3  
Solute carrier family 1 (glial high affinity glut transporter), member 2  
Glutamate-ammonia ligase (glutamine synthase)

## MDD\_DLPPFC

- GABARB2
- GABARG2
- GRIA1
- GRIK5
- SLC1A3
- SLC1A2
- GLUL

GABA A receptor, beta 3  
GABA A receptor, gamma 2  
Glut Receptor, ionotropic, AMPA1  
Glut Receptor, ionotropic, kainite 5  
Solute carrier family 1 (glial high affinity glut transporter), member 3  
Solute carrier family 1 (glial high affinity glut transporter), member 2  
Glutamate-ammonia ligase (glutamine synthase)

Black: Up-regulated; Red: Down-regulated